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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

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02/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,480	SILVER ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,13-17 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,13-17 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 11/3/08. Claims 6, 13-17 and 19-25 are pending and under consideration in this office action.

Response to Amendment

Applicants' amendment has been sufficient to overcome the rejections under 35 USC 112, first and second paragraph.

Claim Objections

Claims 6, 13 and 13 are objected to because of the following informalities: claim 6 recites in the preamble, "method for modulating a target gene in a plant cell said method comprising introducing into said plant cell". The recitation in the second line of "said plant cell" is improper as use of "said" indicates that a previous limitation is being recited. However, the plant cell recited in line 1 has been transformed whereas that recited in line 2 has not been transformed. It would be remedial to amend the second occurrence to --a plant cell-- followed by reference in line 10 and 14 to --the transformed plant cell-- to distinguish between the two.

As well in claims 13 and 14, the recitation of "said plant" suggests that the plant cell is part of a plant, however the claims do not so indicate this relationship. It would be remedial to amend the claim 6 to recite that the plant cell is part of a plant either by being introduced following transformation or as part of a plant during transformation.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 13-17, 19-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating a target gene in a plant cell, said method comprising introducing into a plant cell a first nucleic acid molecule and a second nucleic acid molecule wherein the first nucleic acid molecule comprises a recombinase gene operably linked to an expression control sequence and further comprising two signal sequences recognized by the recombinase encoded by the recombinase gene that flank either the expression control sequences or the recombinase gene and wherein the two signal sequences in the first nucleic acid mediate excision of either the expression control sequences or the recombinase gene in the presence of the recombinase, and said second nucleic acid molecule comprises the target gene and two signal sequences recognized by said recombinase that flank either the target gene or an expression control sequence operably linked thereof wherein the two signal sequences in the second molecule mediate inversion of either the expression control sequences or the target gene wherein if the inverted sequence is the target gene, the expression of said target gene is inactivated and wherein the two signal sequences in the first nucleic acid molecule are not the same as the two signal sequences in the second nucleic acid molecule and wherein the recombinase is expressed, does not reasonably provide enablement for any other embodiment

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without

undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a method for modulating a target gene in plant cell. The target gene is introduced into the cell on a nucleic acid comprising signal sequences that are recognized by a recombinase. In addition a nucleic acid encoding the recombinase is introduced into the cell wherein the nucleic acid comprising the recombinase also comprises signal sequences. In a manner of controlling expression of the target gene, the recombinase mediates inversion of a sequence flanked by the accompanying signal sequences. As well, the same recombinase mediates excision of a sequence on the vector comprising the recombinase. The scope of the invention is extremely broad in that the identity of the recombination signal sequences on either nucleic acid is not characterized, however, the sequences on one nucleic acid mediate excision and on another inversion. As well, the location f the sequences have a profound effect on the resulting reaction, if the sequences do not flank anything critical to modulate expression of either the target gene or the recombinase then the method will not function as required.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ

409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In this case, the broad scope of the claims encompasses a number of inoperable embodiments. First, the structural and functional requirements of the signal sequences on the first and second nucleic acid molecules are critical to functionality of the method and yet the claims lack any guidance on the arrangement or sequence of these sites. As for location, the claims provide functional guidance by reciting that the recombinase "inverts a sequence in said second nucleic acid molecule that is located between said signal sequences in said second nucleic acid molecule, and the inversion results in modulation of expression of said target gene". However, for inversion to occur and for it to result in modulation of expression of the target gene two elements are required. First , the signal sequences must flank either the expression control sequences or the target gene (recombinase) itself. Secondly, the sequences themselves must be arranged such that inversion (excision) is mediated. In fact, the specification teaches, "In one example, two signal sequences in the second nucleic acid molecule are in the same, or direct, orientation with respect to one another. Such signal sequences can, for example, flank the target gene, so that expression of the recombinase results in excision of the target gene and inactivation of expression of the target gene; flank a positive regulatory element of the target gene, so that expression of the recombinase results in excision of the positive regulatory element and inactivation of expression of the target gene; or flank a negative regulatory element of the target gene (endogenous or previously introduced), so that expression of the recombinase results in excision of the negative regulatory element and activation of expression of the target gene.

Alternatively, the signal sequences in the second nucleic acid molecule can be in a different, or an inverted, orientation with respect to one another. Such signal sequences can, for example,

flank an inverted positive regulatory element of the target gene or an inverted coding region of the target gene, so that expression of the recombinase results in inversion of the inverted positive regulatory element or inversion of the inverted coding region, and activation of expression of the target gene. As another example, the signal sequences can flank an inverted negative regulatory element of the target gene or a coding region of the target gene, so that expression of the recombinase results in inversion of the inverted negative regulatory element or inversion of the coding region, and inactivation of expression of the target gene."

Absent this guidance in the claims, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 17, 19, 21-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al. US Patent No. 6,723,896 B1 (previously made of record) in view of Duyk et al (see e.g. 6,531,644; see entire document) or Anderson et al (US 5,849,553; see entire document).

The claims are directed to a method for modulating a target gene in a cell comprising introducing into the cell a first nucleic acid comprising a recombinase gene operably linked to an expression control sequence and signal sequences recognized by a recombinase encoded by the recombinase gene and a second nucleic acid molecule comprising a target gene and signal sequences recognized by the recombinase encoded by the first nucleic acid molecule. The method further requires that the recombinase encode by the recombinase gene in the first nucleic acid molecule, when expressed in the cell, excises a sequence in the first nucleic acid molecule located between the signal sequences, which excision results in modulation of expression of the recombinase gene. In addition, the method requires that the recombinase encoded by the recombinase gene in the first nucleic acid molecule, when expressed in the cell, inverts a sequence in said second nucleic acid molecule that is located between the signal sequences in the second nucleic acid molecule and the excision results in modulation of expression of the target gene, wherein when the sequence inverted in the second nucleic acid molecule is the target gene the expression of the target gene is inactivated. Finally, the claims require that the signal sequences for the first and second nucleic acid are not the same sequences. It is particularly noted that the proviso that expression of the target gene is inactivated is in effect only "when the sequence inverted in the second nucleic acid molecule is said target gene". Therefore, the claim

reads on a method wherein the sequence inverted in the second nucleic acid molecule is other than a target gene and expression of the target gene is activated.

Moller et al. teaches a method of modulating expression of a target gene in a plant cell comprising introducing a nucleic acid comprising a first nucleic acid sequence comprising a Cre recombinase gene operably linked to an expression control sequence and a second nucleic acid sequence comprising a target gene and Lox sequences recognized by Cre recombinase of the first nucleic acid sequence. In one embodiment, the nucleic acid of Moller et al. is configured such that expression of the recombinase in the cell activates expression of the target gene by inverting the gene such that it is in the sense orientation with respect to the promoter sequence comprised by the second nucleic acid molecule. See especially Figure 3 (reproduced herein below), the caption thereto and the first full paragraph in column 6. In this case, the gene is inverted. In so doing, the promoter is inverted and thus activated. The signal sequences in the second nucleic acid molecule are in inverted orientation with one another according to the instant claim 17 (see especially Figure 1); the signal sequences in the first nucleic acid flank both the recombinase gene and positive regulatory elements in the recombinase gene according to the instant claims 21 and 22; the first and second nucleic acid molecules in the construct of Moller et al. are present in the same vector according to the instant claim 23; and teach the Cre/lox system according to claim 25.

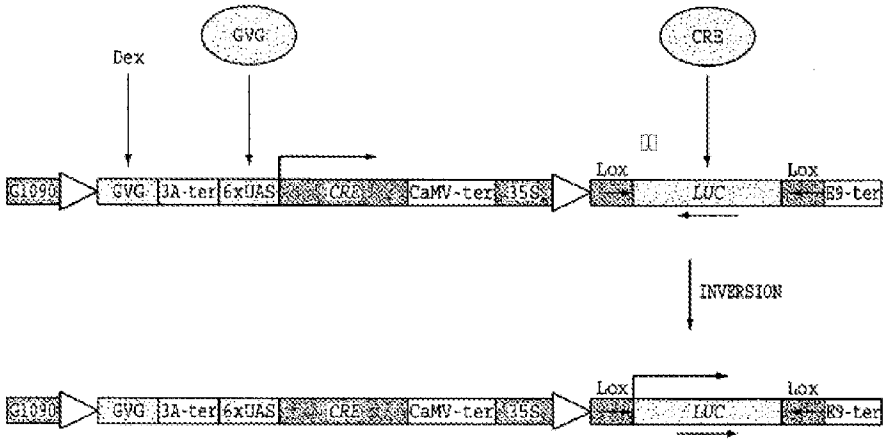

FIG. 3

Moller et al do not teach that the first nucleic acid in addition to comprising a recombinase also comprises signal sequences recognized by the recombinase.

At the time of filing, deletion of the recombinase was demonstrated to be effective. For example, Duyk et al teach that the recombinase gene is introduced into cells flanked by recombinase sequences that are used to delete the gene (see e.g. figure 2 and the legend thereof). As well, Anderson et al teach methods of deleting the recombinase gene by use of flanking site specific recombination sites.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to also include signal sequences flanking the recombinase gene as taught by Duyk et al or Anderson et al in the method of Moller et al. One would be motivated to do so in order to obtain the expected benefit of removal of the recombinase gene as taught to increase stability of the genetic elements. Absent evidence to the contrary, one would have a reasonable expectation of success in using the methods of Duyk et al or Anderson et al in the methods of Moller et al because Moller et al teach that expression of recombinase can be used to inert a target gene to

modify its expression and because Duyk et al and Anderson et al teach that transduced recombinase genes can be introduced on vectors wherein the recombinase gene is flanked by site-specific recombination sites for the deletion of the recombinase gene.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al US Patent No. 6,723,896 B1 in view of Duyk et al (see e.g. 6,531,644; see entire document) or Anderson et al (US 5,849,553; see entire document) et al, as applied to claim 6 herein above, and further in view of Baszczynski et al. US Patent No. 6,187,994 (previously made of record).

Claim 13 is directed to the method of claim 6, wherein the target gene encodes a disease resistance protein. As described above, the method of claim 6, as a whole, would have been obvious to one of ordinary skill in view of the teachings of Moller et al. in view of Duyk et al or Anderson et al. Moller et al and Duyk et al or Anderson et al do not specify that the target gene might encode a disease resistance protein. However, Moller et al. teaches that the system described therein is generally useful for activating transgenes in plants. Baszczynski et al. teaches that it was known in the art at the time of invention that Cre/lox systems for obtaining gene expression could be used to express genes effecting plant susceptibility to disease (i.e., disease resistance genes; see especially the second full paragraph in column 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include disease resistance genes among those expressed by the method of Moller et

al in view of Duyk et al or Anderson et al. One would be motivated to do so in order to obtain the expected benefit of disease resistance in the plant of interest. Absent evidence to the contrary, one would have a reasonable expectation of success in expressing a disease resistance gene by the method of Moller et al in view of Duyk et al or Anderson et al because the method is generally useful for expressing any gene and Baszczynski et al. teaches that genes effecting disease susceptibility could be expressed in plants.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Alternatively Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al US Patent No. 6,723,896 B1 in view of Duyk et al (see e.g. 6,531,644; see entire document) or Anderson et al (US 5,849,553; see entire document) et al, as applied to claim 6 herein above, and further in view of Graham et al (US 6,120,764; see entire document).

Claim 19 is directed to the method of claim 6, wherein the signal sequences flank an inverted positive regulatory element and the inversion results in activation of expression of the target gene. As described above, the method of claim 6, as a whole, would have been obvious to one of ordinary skill in view of the teachings of Moller et al. in view of Duyk et al or Anderson et al. Moller et al and Duyk et al or Anderson et al do not specify that the target gene might encode a disease resistance protein. However, none of the references teach that the regulatory sequence is inverted.

Graham et al teach that expression of a transgene can be driven by inversion of a promoter such that it is active (see e.g. col 15, line 15-54). As well, Graham teaches that the promoter can be inverted to inactivate the promoter.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include disease resistance genes among those expressed by the method of Moller et al in view of Duyk et al or Anderson et al. One would be motivated to do so in order to obtain the expected benefit of disease resistance in the plant of interest. Absent evidence to the contrary, one would have a reasonable expectation of success in expressing a disease resistance gene by the method of Moller et al in view of Duyk et al or Anderson et al because the method is generally useful for expressing any gene and Baszczynski et al. teaches that genes effecting disease susceptibility could be expressed in plants.

In view of the foregoing, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 6, 15-17 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al. US Patent No. 6,723,896 B1 (previously made of record) in view of Odell et al. US Patent No. 5,658,772.

Although Moller et al. teaches activation of the target gene by inversion of the target gene itself, it was known in the art at the time the invention was made that the same end (i.e., activation of a target gene) could be achieved by inverting a promoter or regulatory nucleotide sequence with respect to the target gene. For example, Odell et al. teaches,

> "[F]lipping, occurs when the lox sites are in reverse orientation on the same DNA molecule. This event may provide new methods of cre-regulated gene expression. Gene expression can be turned on by changing the direction of a promoter or regulatory nucleotide sequence from an inactive to an active orientation with respect to a coding region. Also changing the orientation of a coding region with respect to a promoter will alter its expression."

Furthermore, the elements of the dependent claims are also found in the teachings of Odell et al. Specifically, Odell et al. teaches that methods using Cre/lox regulation of gene expression can be used to produce seedless fruit by tissue specific expression of Cre recombinase. (See especially the section bridging columns 13-14, in particular column 14, lines 18-20.) These teachings of Odell et al. render obvious the method of claims 15 and 16. Odell et al. teaches that the nucleic acid comprising the recombinase and the nucleic acid encoding the target gene can be present on separate vectors according to claim 24

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute activation of the target gene by inversion of a regulatory nucleotide sequence for activation by inversion of the target gene in the second nucleotide sequence as taught in the method of Moller et al. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.)

In the instant case, the method of Moller et al. differs from the method of the instant claims in that Moller et al. substitutes inversion of the target gene for inversion of a regulatory element to activate expression of the target gene. However, the teachings of Moller et al. demonstrate that inversion of regulatory sequences by Cre/Lox was recognized in the art as an alternative means of activating expression of target genes in plant cells. Therefore, one of skill in the art could have substituted inversion of a regulatory element for inversion of the target gene in the method of Moller et al. and the substitution would have predictably resulted in activated expression of the target gene. Thus, elements of the claimed method were known to one of ordinary skill in the art at the time the invention was made, one could have substituted one known element for another element known in the art and the substitution would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention. Therefore, practicing the method wherein activation of the target gene is achieved by inversion of a regulatory element in the second nucleic acid molecule would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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